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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,770	06/28/2006	Ronit Sagi-Eisenberg	27514U	5786

20529 7590 12/01/2008

THE NATH LAW GROUP
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EXAMINER	
JUNG, UNSU	
ART UNIT	PAPER NUMBER
1641	
MAIL DATE	DELIVERY MODE
12/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,770	SAGI-EISENBERG, RONIT	
	Examiner	Art Unit	
	UNSU JUNG	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *5,6,15 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,16-26 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species 1 (native rapamycin, claim 2) from List I, species 1b (liquid/blood/mammalian blood, claims 3, 4, and 7) from List II, species 1 (full 12 kDa FKBP12 protein, claim 8) from List III, and species 1aii (FRB fragment directly bound to HRP enzyme and tetramethylbenzidine as the color forming reagent, claims 14, 16-19, and 23-26) in the reply filed on July 29, 2008 is acknowledged.

Claims 1-4, 7-14, 16-26, and 31 read on the elected species. Therefore, claims 5, 6, 15, 27-30, and 32 have been withdrawn from consideration.

Status of Claims

2. Claims 1-32 are pending, claims 5, 6, 15, 27-30, and 32 have been withdrawn from consideration, and claims 1-4, 7-14, 16-26, and 31 are currently under consideration for patentability under 37 CFR 1.104.

Priority

3. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/IL04/01172, filed December 29, 2004 and U.S. Provisional Application Serial No. 60/532,552 filed December 29, 2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this

application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge

under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on July 29, 2008 has been considered by the examiner.

Specification

5. The use of the trademark SEPHAROSE® (p12, line 7) and TALON® (p12, line 26) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-4, 7-9, 13-17, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane et al. (U.S. Patent No. 5,650,288, July 22, 1997) (hereinafter "MacFarlane") in view of Chen et al. (U.S. Patent No. 4,385,126, May 24, 1983) (hereinafter "Chen") and Clackson et al. (U.S. Patent No. 6,187,757, Feb. 13 2001) (hereinafter "Clackson").

MacFarlane teaches that a major concern in immunosuppressive therapy associated with organ transplantation is the level of immunosuppressive drug circulating in the blood (see entire document, particularly column 1, lines 40-42). Toxicity can result if the immunosuppressive drug level is too high; graft rejection and opportunistic infection can result if the immunosuppressive drug level is too low (column 1, lines 42-45). MacFarlane et al. provides a method of assaying a sample of blood or blood components for the concentration of immunophilin ligand such as rapamycin using a variety of binding assays including receptor binding assay (column 2, lines 6-24).

With respect to claims 3, 4, and 7, MacFarland et al. teaches a sample, which is a clinical blood sample (column 1, lines 14-45).

With respect to claims 20 and 21, MacFarlane teaches a kit containing reagents for detection assay of immunophilins (column 6, lines 20-34).

With respect to claim 31, MacFarlane teaches use of standards, which would read on "pre-weighed samples of rapamycin" (column 5, line 61).

However, MacFarlane et al. fails to teach a method, wherein the receptor binding assays includes a sandwich format using immobilized FKBP12 and mTOR as a detecting receptor.

Chen teaches a well known method of sandwich assay, in which an assay ligand binds to an immobilized receptor ligand to form a first complex (see entire document, particularly column 1, lines 40-42). A tagged test ligand is then bound to the assay ligand in the complex to form the sandwich and the tagging constituent in the sandwiched ligands is detected quantitatively to deduce the quantity of assay ligand present. The detection can be performed by measuring radioactive, fluorescent, or enzyme labels present on the test ligand (column 1, lines 42-47). Furthermore, the quantity of assay ligand is deduced from quantity of test ligand detected using known standards (column 1, lines 58-62).

With respect to claims 13, 14, 16, 17, and 22-25, Chen et al. teaches that the test ligand (FRB fragment of Clackson set forth below) is directly bound to a detectable label/enzyme, which can be detected by spectrophotometry, fluorospectrophotometry, and radiospectrometry (column 1, lines 42-47).

With respect to claims 7-9, Clackson teaches that rapamycin binds to a FK506-binding protein (FKBP12, see entire document, particularly column 4, lines 57-62) with high affinity to form a rapamycin:FKBP complex, which binds with high affinity to the FRB domain of large cellular protein FRAP (mTOR, column 7, lines 56-67) to form FKBP:rapamycin:FRAP complex (column 1, lines 13-21). A number of rapamycin variants have been synthetically produced to improve the compound's therapeutic index as an immunosuppressive agent (column 2, lines 4-7).

With respect to claims 13-14, and 22, Clackson teaches FRB fragment (column 95, line 53).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to utilize a sandwich assay method of Chen, which employs two receptors for a detection ligand using a standard curve, in the method of assaying a blood sample for immunosuppressive drug, rapamycin, as taught by MacFarlane in order to perform an assay to detect concentration of rapamycin using FKBP12 and mTOR of Clackson, which are known protein receptors of rapamycin. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use FKBP12 as the immobilizing receptor since FKBP12 binds to the rapamycin independent of mTOR, while mTOR binds to the FKBP12-rapamycin complex as taught by Clackson.

The advantage of using the sandwich assay method, which is well known in the binding assay art to be one of the most sensitive assays for detecting target analytes in the sample, provides the motivation for combining the methods of Chen Clackson, and MacFarlane as the two rapamycin binding proteins, FKBP12 and mTOR, have high affinity for rapamycin.

One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining teachings of Chen, Clackson, and MacFarlane since MacFarland teaches that a variety of binding assays including receptor binding assay can be used to determine level of immunosuppressive drug circulating in the blood.

With respect to claim 2, Clackson et al. teaches that a variety of rapamycin analogs (synthetic) are used as a therapeutic agent (column 2, lines 4-22) and also bind

to FKBP12 (column 4, lines 57-62) and mTOR (column 7, lines 31-67). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to determine the concentration of rapamycin or rapamycin analog in patients in order to determine rapamycin analog levels in patients receiving rapamycin analogs as FKBP12 and mTOR form FKBP:rapamycin:FRAP complex in the presence of rapamycin or rapamycin analogs.

9. Claims 10, 12, 18, 19, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13, 2001) as applied to claims 1, 3, 20, 22, and 25 above, and further in view of Hammock et al. (U.S. Patent No. 5,459,040, Oct. 17, 1995) (hereinafter "Hammock").

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above. However, MacFarland in view of Chen and Clackson fails to teach a method, wherein the solid support is a 96-well microtiter plate and the detection is achieved by an ELISA reader and the enzyme is horse radish peroxidase (HRP).

With respect to claims 10, 12, 18, 19, and 26, Hammock teaches that sandwich assay can be conducted using 96-well microtiter plates (see entire document, particularly column 5, lines 24-26) and that variety of different labels including HRP can be used for detection (column 10, lines 30-51). The 96-well microtiter plates can be

read by ELISA plate readers (column 11, line 52-column 12, line 8) following color development using chromogenic substrates such as 3,3',5,5'-tetramethylbenzidine (column 10, lines 30-51).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ a 96 well microtiter plate, which detected by an ELISA reader, wherein HRP is used as an enzyme label with 3,3',5,5'-tetramethylbenzidine as a substrate as taught by Hammock in the method and kit of MacFarland in view of Chen and Clackson in order to perform sandwich assay for determining rapamycin concentrations in a sample.

The advantage conducting multiple sample analysis of rapamycin using 96-well microtiter plate with an ELISA reader, which is designed for reading 96-well plate, provides the motivation for combining the methods of MacFarland in view of Chen and Clackson.

In addition, one of ordinary skill in the art would have found it obvious to employ the HRP as an enzyme label with 3,3',5,5'-tetramethylbenzidine as a substrate as taught by Hammock since it appears that any well know enzyme label and corresponding substrate such as HRP and p3,3',5,5'-tetramethylbenzidine would perform equally well with the assay method of MacFarland in view of Chen and Clackson.

10. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13,

2001) as applied to claims 1 and 3 above, and further in view of Coligan et al. (Current Protocols in Immunology, Vol. 1, 1991, John Wiley & Sons, Inc., pp2.1.1-2.1.22) (hereinafter "Coligan").

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above. However, MacFarland in view of Chen and Clackson fails to teach a method, wherein the solid support is a 96-well microtiter plate, which is blocked by non specific protein, and the detection is achieved by an ELISA reader.

Coligan et al. teaches methods of variety of sandwich assays, which are typically conducted on a 96-well microtiter plates and read by an ELISA reader (p2.1.17, Fig. 2.1.7). Coligan et al. further teaches a blocking step, which blocks residual binding capacity of the plate following immobilization of capture antibody (p2.1.5, Block residual binding capacity of plate).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ a 96 well microtiter plate, which is blocked by non specific protein and detected by an ELISA reader, as taught by Coligan in the method of MacFarland in view of Chen and Clackson in order to perform sandwich assay for determining rapamycin concentrations in a sample.

The advantage conducting multiple sample analysis of rapamycin using 96-well microtiter plate with an ELISA reader, which is designed for reading 96-well plate, provides the motivation for combining the methods of MacFarland in view of Chen and Clackson and Coligan.

Furthermore, one of ordinary skill in the art at the time of the invention would have recognized that blocking step of Coligan et al. is a necessary step in a sandwich assay to block binding of non specific proteins. Therefore, the advantage of including a blocking step in order to block binding of non specific proteins provides the motivation for combining the methods of MacFarland in view of Chen and Clackson and Coligan as the blocking step would increase the specificity of the assay of MacFarland in view of Chen and Clackson.

11. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13, 2001) as applied to claims 20 and 22 above, and further in view of Abuknesha (U.S. Patent No. 5,723,304, Mar. 3, 1998).

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above. Clackson et al. further teaches that a variety of rapamycin analogs (synthetic) are used as a therapeutic agent (column 2, lines 4-22) and also bind to FKBP12 (column 4, lines 57-62) and mTOR (column 7, lines 31-67). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to determine the concentration of rapamycin or rapamycin analog in patients in order to determine rapamycin analog levels in patients receiving rapamycin analogs as FKBP12 and mTOR form FKBP:rapamycin:FRAP complex in the presence of rapamycin or rapamycin analogs.

Abuknesha teaches that analyte species or analyte analog species can be used as standard or calibrator (column 1, line 58-column 2, line 2).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to further include rapamycin analogs as known standards with a reasonable expectation of success in order to determine rapamycin and/or rapamycin analog concentrations in a sample since Abuknesha teaches that analyte species or analyte analog species can be used as standard or calibrator.

Prior Art of Record

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Molnar-Kimber et al. (U.S. Patent No. 5,504,091, Apr. 2, 1996) teaches a receptor based assay to measure rapamycin levels using a rapamycin-binding protein, wherein wells of microtiter plates are coated with a fusion protein comprising FK506 binding protein (see entire document). A standard curve was generated to determine concentration of rapamycin in a sample.
- McBeath et al. (U.S. PG Pub. No. US 2002/0102617 A1, Aug. 1, 2002) teaches a method of performing an assay for detection of small molecules (p8, paragraph [0065]) such as rapamycin (see entire document, particularly p3, paragraph [0018]) using protein arrays, wherein proteins are covalently or non-covalently attached to the surface of a solid support

and retain their ability to interact specifically with other proteins, polynucleotides, other biological macromolecules, or small molecules (Abstract). In screening for protein-protein interaction or for protein targets of known proteins, any proteins may be used on the microarrays or in the assay method and the interactions may be detected via any method known in the art including fluorescence, radioactivity, immunoassay, etc. (p6, paragraph [0052]). The microarray of McBeath et al. allows for high density arrays of proteins while preserving proteins' functions (p1, paragraphs [0005] and [0006]).

- Gingras et al. (*Genes & Dev.*, 2001, Vol. 15, pp807-826) teaches that FK506 binding protein (FKBP12), which is abundant, ubiquitously expressed protein, is the primary intracellular rapamycin receptor (p809, Rapamycin target proteins, second paragraph) and a mammalian homolog of target of rapamycin (mTOR), which binds to FKBP12-rapamycin complex via FKBP12-rapamycin binding (FRB) domain (p810, Modular structure of the Tors and FRAP/mTOR, third paragraph).

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
Unsu Jung
Patent Examiner
Art Unit 1641